REMARKS

The status of the claims is as follows:

Original:	4-8, 12 and 14
Currently amended:	1, 3, 9-11, 13, 15 and 16
Previously presented:	18 and 20
Canceled:	2, 17 and 19
Withdrawn:	18 and 20

Claims 1, 3-16, 18 and 20 will be pending with entry of this amendment.

The specification has been amended on page 32 to change the reference to "protease" in line 27 to "integrase". This is an obvious error in that the description as a whole makes it clear that the compounds of the invention are HIV integrase inhibitors.

The structure appearing in Example 3 on page 62 of the specification has been amended to more clearly show that the CH_3 group is attached to position 7 of the dihydropyridopyrazine ring.

The final reaction step depicted in Scheme 8 on page 53 has been amended to make it more clear that the variable in the acyl substituent on compound **8-4** is "R^" and not: "R".

The definition of R^1 in claim 2 has been incorporated into claim 1, claim 2 has been canceled, and claim 3 has been amended to refer to claim 1.

The term "aryl" in claim 1 has been amended to refer to phenyl or naphthyl. Support for this amendment can be found on lines 26-27 on page 34.

The other claim amendments are described below. None of the amendments herein introduces new matter.

Correction of Inventorship under 37 CFR § 1.48

A request for correction of inventorship under Rule 1.48 accompanies this amendment.

Information Disclosure Statement

An information disclosure statement (IDS) accompanies this amendment. The information disclosure statement lists US 2005/0288293 which corresponds to co-pending serial no. 10/526,280 which has the same effective filing date as the subject application. The IDS also lists from co-pending serial no. 10/526,280 the office action mailed November 28, 2007, the amendment filed February 27, 2008, and the notice of allowance mailed April 4, 2008. Copies of office action, the amendment and the notice of allowance are enclosed with the IDS. It is

requested that the Examiner consider the information listed in the IDS, make the information of record, and return an initialed copy of the IDS with the next communication to Applicants.

Interview

In a telephonic interview conducted April 23, 2008 between the Examiner and the undersigned, the undersigned found the text in the office action concerning the traversal of the restriction requirement confusing. The Examiner verified that applicant's traversal of the restriction requirement is persuasive in part such that Group VIII is rejoined with elected Group IV. Nothing else was discussed in the interview.

Restriction Requirement

Per the April 23rd interview discussed above, the Examiner rejoined Group VIII with elected Group IV. The claims have been amended herein to remove non-elected subject matter. Applicants reserve the right to pursue the removed subject matter in one or more continuing applications.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-16 have been rejected under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification. Without conceding the correctness of this rejection, the claims have been amended to reduce their scope. More particularly, the definition of R^1 in claim 2 has been incorporated into claim 1, and claim 2 has been canceled; and the term "aryl" in claim 1 has been amended to refer only to phenyl or naphthyl. In addition, as a result of complying with the restriction requirement, the alternative definitions of R^2 and R^3 have been removed from claim 1, and the alternative definitions of $R^{2'}$ and $R^{3'}$ have been removed from claims 9-11 and 13. This rejection is traversed with respect to the claims as amended herein.

The specification provides sufficient disclosure to enable a person of ordinary skill in the art to make and use the compounds as set forth in claims 1 and 3-15 and the pharmaceutical composition recited in claim 16 without undue experimentation. More particularly, the specification discloses that HIV is the etiological agent responsible for AIDS (page 1, lines 17-20), that integration of the proviral DNA into the host cell genome is a required step in HIV replication (page 1, lines 21-24), and that HIV integrase, the enzyme mediating the integration of the proviral DNA, is one of the enzymes that has been shown to be essential for the replication of HIV (page 1, lines 32-35).

In addition, the specification describes in detail the elected dihydroxydihydro-pyridopyrazine-1,6-dione compounds and embodiments and classes thereof (pages 3-31), and discloses that the compounds are useful in the inhibition of HIV integrase, the treatment of infection by HIV, the treatment of AIDS and the delay in the onset of AIDS (page 3, lines 2-7; page 38, lines 6-16). The specification provides comprehensive guidance and directions on how

to prepare the elected compounds via Schemes 1-6 and 8-10 on pages 46-55 and via Examples 1-24, 31-38 and 44. The specification further discloses that compounds representative of the claimed 1,6-diones have been shown by testing in suitable assays to inhibit HIV integrase (Example 49) and to inhibit the replication of HIV (Example 50).

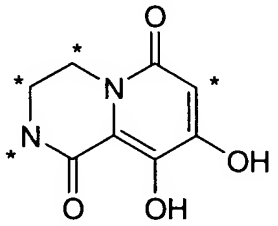
The specification also discloses means for administering the claimed compounds (page 39, lines 17-23), provides guidance on the preparation of pharmaceutical compositions for administration of the compounds including a cite to the 18th edition of Remington's Pharmaceutical Sciences (page 40, lines 11-17), and provides guidance on suitable dosage ranges for oral administration of the compounds (page 40, lines 18-32).

Applicants' position is that this disclosure is sufficient to enable the rejected claims as amended herein. More particularly, using this description, optionally in combination with know-how available in the art, the person of ordinary skill can without undue experimentation prepare and administer a compound of the invention in a suitable carrier and in the appropriate dosage form and dosage amount to a subject in order to inhibit HIV integrase, treat HIV infection, treat AIDS, or delay the onset of AIDS.

The following are detailed remarks addressing assertions made in the Office Action:

1. The Examiner has asserted that Applicants have provided no guidance, examples, or data for compounds of Formula I other than those in which R^1 is optionally substituted benzyl and R^2, R^3 and R^4 are H or optionally substituted alkyl. Applicants disagree. As noted above, the application provides a series of generic preparative schemes and detailed examples. The schemes provide sufficient direction for preparing the compounds embraced by the claims. Furthermore, as stated in the application (page 57, lines 8-10), the specific examples do not limit, but instead illustrate the invention and its practice. It is understood that the schemes and examples do not provide explicit directions for making all compounds embraced by the claims, but they do provide sufficient guidance such that the skilled artisan can make the claimed compounds without undue experimentation. As noted in the application, in light of these schemes and examples, those of ordinary skill in the art will be able to use known variants thereof and other preparative methods that would be readily apparent therefrom to make compounds of the invention. For example, from the combination of Schemes 2 and 3 it would be readily apparent to the skilled artisan that compounds of Formula I in which R^1 is C_{1-4} alkyl substituted with aryl group (which itself is optionally substituted) can be made by employing a suitable arylalkyl halide in place of benzyl halide **3-2** in Scheme 3 and then employing the arylalkyl substituted analog of **2-1** obtained from Scheme 3 in Scheme 2. More generally, the schemes and examples collectively describe how to build the dihydroxydihydro-pyridopyrazine-1,6-dione core of the claimed compounds with various substituents attached thereto. Using this disclosure in combination with his/her general chemical knowledge, the skilled artisan can prepare the core with other substituents for which no explicit example is provided.

Turning to the issue of whether there is sufficient data to guide the use of the claimed compounds, it is first noted that the specification discloses that representative compounds of the invention exhibit inhibition of strand transfer activity in HIV integrase (Example 49) and inhibition of HIV replication (Example 50). Representative compounds of the invention include the compounds set forth in Examples 1-24, 31-38 and 44 which were determined to have IC_{50} values less than 5 μM in the strand transfer assay and IC_{95} values less than 10 μM in the replication inhibition assay. The compounds in these Examples all have the following common core where the asterisks denote the location of substituents:



The person of ordinary skill in the art at the time the application was filed would believe that this core structure is the basis for the integrase inhibition activity and HIV replication inhibition activity of these compounds and would accordingly understand that the activity exhibited by the compounds in the Examples can be expected for other compounds embraced by the instant claims, all of which have the same core. The activity of the compounds embraced by the claims would vary with the type and number of substituents attached to the core, but the skilled artisan would expect the claimed compounds to share the same physiological activity as the exemplified compounds.

2. The Examiner has noted that "chemistry is unpredictable". The question here is not whether chemistry in general is unpredictable, but is instead whether or not the subject application provides sufficient disclosure to permit the skilled artisan to make the claimed compounds without undue experimentation. As already explained above, the application offers sufficient guidance to permit the skilled artisan to make the compounds without undue experimentation or, put another way, to make the compounds with a reasonable degree of predictability.

3. The Examiner has asserted that the claims are "very broad". The claims as amended herein are narrower in scope than the original claims, and for reasons already given above, it is Applicants' position that the amended claims are enabled.

In view the amendment to the claims and the foregoing remarks, withdrawal of this rejection is requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claim 15 has been rejected as being indefinite due to the use of the phrase "and pharmaceutically acceptable salts thereof." This rejection is traversed. Claim 15 is a list of alternatives presented as a Markush group, wherein the use of "and" is standard practice. See, e.g., MPEP 2173.05(h). Withdrawal of the rejection is requested.

Claim 16 has been rejected as being indefinite due to the use of the phrase "therapeutically effective amount of ". The offending phrase has been removed from the claim. Withdrawal of the rejection is requested.

The application is believed to be in condition for allowance and passage to issue is requested. The Examiner is invited to telephone the undersigned should any minor matters need to be resolved before a Notice of Allowance can be mailed.

Respectfully submitted,

By: Kenneth R. Walton

Kenneth R. Walton, Reg. No. 32,951
Attorney for Applicants
MERCK & CO., Inc.
P.O. Box 2000
Rahway, New Jersey 07065-0907
Tel.: (732) 594-3462

Date: May 20, 2008